REMARKS

A check for the fee for a two-month extension of time is attached hereto. Also attached is a Change of Correspondence Address for the undersigned. Any fees that may be due in connection with this application may be charged to Deposit Account No. **06-1050**. If a Petition for extension of time is needed, this paper is to be considered such Petition.

In a note regarding the previous amendment, claim 66, although not marked as amended in the previous amendment, was amended to change dependency from depending on claim 60 to depending on claim 64, as currently recited. The error in failing to note the amendment was inadvertent and the amendment did not add new matter.

Claims 1-6, 9-34, 40-51, 54-61 and 63-72, 78, 82-94 and 102-107 are pending in this application. Claims 5, 13, 18, 25, 28-30, 32-40, 41, 45, 46, 49, 50, 55, 71, 72, 83 and 87 are amended and claims 102-107 are amended to more particularly point out and distinctly claim the subject matter by correcting obvious inadvertent errors in antecedent basis and other minor inconsistencies. Basis for the amendments can be found throughout the application as originally filed. For example, basis for the amendment of claim 5 is found in the specification, for example, at page 6, first full paragraph, and at page 25, top paragraph; basis for the amendment of claim 40 can be found in the specification, for example, at page 27, second paragraph; basis for the amendment of claim 46 can be found at page 6, last paragraph.

Basis for claims 102-107 can be found throughout the specification. Particular basis can be found, for example at page 5, which recites:

> The substrates can be silicon, metal, plastic, a membrane, polymeric material, a metal-grafted polymer, as well as a substrate that is functionalized chemically, functionalized with beads, functionalized with dendrite trees of captured material, or any combinations of the above or any similar suitable material for receiving the dispensed fluid.

Therefore no new matter is introduced.

THE REJECTION OF CLAIMS 43 AND 44 UNDER 35 U.S.C. §112, FIRST PARAGRAPH FOR LACK OF ENABLEMENT

Claims 43 and 44 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable one skilled in the art to practice a claim that does not recite the presence of analyte in a fluid containing solvent and matrix. This rejection is respectfully traversed.

RELEVANT LAW

In order to satisfy the enablement requirement of 35 U.S.C §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

ANALYSIS

It is respectfully submitted that the application teaches those of skill in the art how to dispense volumes of a material as an array onto the surface of a substrate, as recited in claims 43 and 44, without requiring analyte to be dispensed along with solvent and matrix. For example, the specification, at page 6, last paragraph, teaches first dispensing fluid containing matrix onto a substrate, waiting for the solvent to evaporate, and then adding analyte fluid to the evaporated matrix material. The specification, for example, at the paragraph spanning pages 20-21, teaches methods in which analyte is first dispensed onto a substrate, followed by matrix solution, and methods of dispensing pre-mixed matrix and analyte solutions. It is these embodiments to which claims 43 and 44 are directed.

The Office Action appears to assert that claims 43 and 44 lack enablement because the claims fail to recite an allegedly critical element. To assess this, it is necessary to consider the entire teachings of the specification to determine whether an unclaimed feature is critical (*In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)). Further, an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim "should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended." (MPEP §2164.08(c)). Broad language in the specification tends to rebut the argument of criticality.

Claims 43 and 44, and claim 40 from which they depend, recite dispensing fluid containing a material onto a substrate. As is apparent from the specification as discussed above, the dispensed fluid can contain matrix or analyte, or both. The specification supports this by teaching a variety of dispensing protocols. For example, the specification teaches that matrix can be dispensed onto a substrate alone or mixed with analyte. Further, the specification teaches that matrix can be dispensed onto a substrate prior to dispensing an analyte, subsequent to dispensing an analyte, or simultaneously with an analyte. Matrix can be dispensed alone and permitted to evaporate on the substrate; substrate can be added later by a user of the resulting array of matrix material. Alternative embodiments in which analyte is dispensed and the order in which matrix is dispensed is varied are recited in dependent claims, such as claim 47-50. Claims 43 and 44 are directed to embodiments in which matrix is dispensed before analyte. Requiring claims 40, 43 or 44 to recite dispensing analyte along with matrix would alter scope that is supported by the specification.

THE REJECTION OF CLAIMS 1-4, 6, 9, 10, 14, 15, 25-28 and 30 UNDER 35 U.S.C. § 102(b)

Claims 1-4, 6, 9, 10, 14, 15, 25-28, and 30 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Zhang *et al.*, *J. Mass Spec. 30*:1768-

1771 (19950 because Zhang *et al.* allegedly discloses dispensing material on a multi-well sample holder by moving a vesicle from spot to spot and ejecting a defined and controlled volume of fluid such that MALDI spectra obtained from the spots are reproducible. The Office Action also appears to indicate that the reference discloses that the vesicle does not touch the sample holder, basing this conclusion on the fact that the reference does not disclose contacting the vesicle with the sample holder. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure of each element of the claim under consideration in a single prior art reference. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Disclosure of the cited reference and differences from the instant claims

A close reading of Zhang *et al.* reveals that its disclosure is very different from the instant claims. Zhang *et al.* is directed to a method for concentrating and desalting samples. Zhang *et al.* does not describe deposition of defined and controlled volumes nor disclose a method that requires such precision in sample deposition, not in a high throughout analyses requiring reproducibility among mass spectra on an array on single surface. As described in the DECLARATION of record in this case, the substrates are for use in high throughput screening methods that require reproducibility among samples at each locus in order to identify small differences, such as SNPs. Zhang *et al.* does not even address or describe arrays nor mention high throughput analyses. Furthermore, Zhang *et*

al. does not disclose deposition of a plurality of samples; only elution of material from a column.

Zhang *et al.* describes the problems in detecting samples present at low concentrations and the a desalting method following concentration of samples. Zhang *et al.* discloses a sample concentration and desalting procedure for improving mass spectra of compounds that are present at attomole or femtomole levels in relatively large volumes of solutions too dilute for detection. Zhang *et al.* states that concentration can result in material that contains high concentrations of salt that interfere with MALDI mass spectra acquisition. Zhang *et al.* provides a method for concentrating and desalting small sample volumes using a capillary column containing C_{18}-packed fused-silica capillary for micro-concentration and desalting. A system containing this capillary as well as means for matrix addition and dispensing of column eluate onto a surface also are disclosed. Samples are loaded onto the capillary column by injection through a 10 μl loop and loaded on to the C_{18}-packed capillary. The column is washed and the analyte material binds to the column. As with any such column desalting procedure, if the material is quantitatively eluted, the eluted volumes are not critical for accuracy. For example, if a 10 μl sample is loaded onto the column and it contains, for example, 1 pg of material, the 1 pg of material is bound to the column, which is then washed to remove unbound material and then the bound material is eluted.

The particular elution volume is based upon properties of the column; the goal generally is to elute all of the material, whether it is in 1 μl or 5 μl or more or less. Typically (and Zhang *et al.* is not quite clear) fractions are collected and the eluate in fractions is monitored until all material is eluted. Alternatively, a step gradient can be used to elute material, which can be collected in a single fraction. The particular elution buffer and conditions can be selected so that enough elution buffer is added for quantitative elution in single fraction (which appears to be what Zhang *et al.* discloses). Such volume will be chosen to be

more than enough to quantitatively elute the material. So, for example, Zhang *et al.* could have determined that 4 μl of elution buffer was sufficient for quantitative elution, so that use of about 5 μl will remove all bound material. It is apparent, that it does not matter whether 4 μl or 4.5 μl or 5 μl or 6 μl volume is used - the amount of material is the same. Hence, Zhang *et al.* discloses that "about 5 μl" is dispensed.

No where in Zhang *et al.* is there a statement that precision in the volume of material deposited on a substrate is important. There is no need for defined and controlled volumes, since the amount of analyte material dispensed is not critically dependent upon the eluate volume. Thus, it is very clear that Zhang *et al.* does not disclose, teach or suggest dispensing a defined and controlled volume but rather teaches a desalting method in which analyte is quantitatively eluted from a column. In such instances, the volume dispensed is not important; rather it is important to quantitatively elute all material and such volume has to be some minimum but larger volumes or a variation in volume is not critical. Zhang *et al.* does not address the issue of depositing defined and controlled volumes nor disclose how such is to be achieved. Furthermore, Zhang *et al.* does not disclose preparation of arrays nor any mention of reproducible spot size.

The eluate is directly spotted onto a sample holder. The resulting volume is stated to be "*about* 5 nl per fraction." This belies any conclusion that Zhang *et al.* discloses dispensing defined and controlled volumes or produces a substrate with spots that results from such deposition such that mass spectra at each spot are reproducible within the array of spots. There is no explicit nor implicit disclosure in Zhang *et al.* that would place the public in possession of such disclosure. In fact, as noted, in practicing the method as described by Zhang *et al.* **there is no need for the volume dispensed to be defined and controlled**, because Zhang *et al.* is concerned with the amount and condition of the sample eluted (*i.e.*, concentrated and desalted sample), not the volume of

eluant used to elute the sample nor the volume of eluant dispensed onto the target.

Zhang *et al.* states that the desalting and concentration "increased the MALDI sensitivity for dilute peptide samples," and an increase in signal to noise ratio was observed for the desalted samples compared to the untreated samples. Zhang *et al.* states that the desalting procedure permits quantitative determination of peptide (*i.e.*, discusses the sensitivity of the method; not reproducibility among spots on a substrate that contains a plurality of such samples). Zhang *et al.* suggests nothing regarding delivery of defined and controlled volumes nor reproducibility among spectra from spots on an array. Zhang *et al.* is directed to increasing the sensitivity of MALDI, not reproducibility.

Thus, Zhang *et al.* does not disclose a method in which vesicles dispense "defined and controlled volumes" nor methods for producing arrays of spots such that spot-to-spot mass spectra are reproducible among the array of spots, nor methods in which dispensing is achieved using vesicles that do not touch the surface of the substrate. Zhang *et al.* does not disclose moving a vesicle to a second position next to the first location or to a set of positions. Zhang *et al.* does not disclose an array of spots of sample material on the substrate such that spot-to-spot characteristics are reproducible in a spot array. Zhang *et al.* does not disclose performing mass spectrometry analysis at each location of an array. Zhang *et al.* does not disclose that mass spectra obtained from each spot of an array that are reproducible within the array of spots; Zhang *et al.* does not disclose an array of spots.

The Claims

Claim 1

Independent claim 1 is directed to:

> A method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material;

disposing said vesicle adjacent to a first location on said surface of the substrate *without contacting the surface with the vesicle*;

providing mechanical pressure to the interior of the vesicle to eject from said chamber a *defined and controlled 0.2 to 20 nanoliter volume* of the fluid to dispense said fluid at said first location of said surface of the substrate;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled 0.2 to 20 nanoliter volume of fluid is dispensed at each location of said set forming an array of spots of sample material on the substrate such that spot-to-spot characteristics are reproducible in the array; and

performing mass spectrometry analysis of the sample material at each location of the array, wherein *mass spectra of the sample obtained from each spot are reproducible within the array of spots*.

Claim 25

Independent claim 25 is directed to:

A method for analyzing a material, comprising:

providing a vesicle comprising a fluid containing the material in a solvent;

disposing said vesicle adjacent to a first location of a surface of a substrate without contacting the surface with the vesicle;

delivering a *defined and controlled nanoliter volume* of the fluid at the first location of said surface of the substrate;

moving said vesicle to a second position next to the first location on said surface of the substrate to dispense a defined and controlled nanoliter volume of said material along an array of locations on said substrate surface *to form an array of the material such that spot-to-spot characteristics are reproducible in the array*; and

performing mass spectrometry analysis for said material at each location of said array, wherein mass spectra of the material obtained from each spot are reproducible within the array of spots.

All other claims rejected under U.S.C. §102(b) depend from claims 1 and 25, and thus contain all elements of the respective independent claim.

Analysis

It is respectfully submitted that Zhang *et al.* does not disclose all elements of the claimed methods. The cited reference does not disclose a vesicle disposed adjacent a substrate without contacting the substrate. The cited

reference does not disclose dispensing a defined and controlled volume to form an array of spots having reproducible spot-to-spot characteristics such that mass spectra within an array of spots are reproducible. The cited reference also does not disclose moving a vesicle to two or more position nor delivery of the defined and controlled volume without contacting the surface. Each limitation and requirement of the claims is discussed in turn.

"Without contacting"

Claims 1 and 25 recite disposing a vesicle adjacent to a first location on the surface of a substrate without contacting the surface. Zhang *et al.* does not disclose a method in which a vesicle is disposed adjacent to the substrate without contacting the surface of a substrate. Zhang *et al.* provides no guidance on the procedure for transferring eluate from the C_{18}-packed capillary to the target. Zhang *et al.* provides no guidance for a device used for dispensing fluid onto the target. Zhang *et al.* only discloses that sample was spotted onto a target. Thus, Zhang *et al.* does not inform one of ordinary skill in the art whether eluate was spotted on the target by contacting the target or whether eluate was spotted on the target by not contacting the target.

The Office Action, in attempting to establish that Zhang *et al.* discloses this claim element, states, "No contacting of the vesicle with the substrate for disposing the liquid is indicated in the paper." No further support is provided by the Office Action. The standard for a rejection based on U.S.C. §102 is: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The Office Action fails to point to any express disclosure of Zhang *et al.* of not contacting the target. Moreover, Zhang *et al.* has no such disclosure. Thus, the Office Action presumably is asserting that not contacting the target is inherently disclosed by Zhang *et al.*

In attempting to establish a claim element as inherently disclosed, it is insufficient to simply point to a lack of a disclosure. To establish inherency, the evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. MPEP §2112; *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). In order to rely upon the theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP §2112; *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

The Office Action has provided no basis in fact or technical reasoning that Zhang *et al.* inherently discloses disposing a vesicle without contacting the surface of a substrate. Thus, the Office Action does not reasonably support the position that disposing the vesicle without contacting the surface of the substrate necessarily flows from the disclosure of Zhang *et al.* Moreover, no such basis for inherency exists. The disclosure of Zhang *et al.* does not inform one of ordinary skill in the art whether eluate was spotted on the target by contacting the target or whether eluate was spotted on the target by not contacting the target. Thus, one of ordinary skill in the art would not consider disposing the vesicle without contacting the target to necessarily flow from the disclosure of Zhang *et al.* Because disposing the vesicle without contacting the target does not necessarily flow from the disclosure of Zhang *et al.*, the cited reference cannot inherently disclose this claim element. In essence, Zhang *et al.* discloses a genus in which material is dispensed, but does not recite particular

species thereof (contact target or not contact target). A genus never anticipates a species.

Thus, Zhang *et al.* neither expressly nor inherently discloses disposing the vesicle without contacting the surface of the substrate, as recited in claims 1 and 25. Therefore, Zhang *et al.* cannot anticipate claims 1 or 25, or claims dependent therefrom.

Dispensing a Defined and Controlled Volume to Form an Array of Spots Having Reproducible Spot-to-Spot Characteristics

Furthermore, Zhang *et al.* does not anticipate any of the pending claims because it does not disclose delivery of a defined and controlled volume nor delivery such that mass spectra among the spots are reproducible in an array of spots.

Zhang *et al.* discloses a method for concentrating and desalting a sample for mass spectrometry. The method of Zhang *et al.* is directed to sample preparation, not a to method for forming an array of spots with reproducible spot-to-spot characteristics. In Zhang *et al.*, there is no need for the volume dispensed to be defined and controlled, because Zhang *et al.* is concerned with the absolute amount and condition of the sample eluted (i.e., concentrated and desalted sample), not the volume of eluant used to elute the sample nor the volume of eluant dispensed onto the target. As such, the only details of the substrate disclosed by Zhang *et al.* provide that, using syringe pumps with an elution rate of 0.1 μL/min., $\sim$5 nL of eluate was spotted onto the substrate. Zhang *et al.* does not disclose forming an array of spots where each spot results from deposition of a defined and controlled volume.

Despite disclosing elution at 0.1 μL/min., Zhang *et al.* does not disclose any method for controlling the time length for delivery of the eluate to the substrate. For example, the eluate could have been deposited by an individual estimating a delivery time length of 3 seconds, which could result in a substrate with irreproducible spot size, but the spot would still be suitable if elution were quantitative. Further, Zhang *et al.* does not disclose a method or vesicle for

delivering the eluate. By not disclosing a method and apparatus for sample deposition, Zhang *et al.* fails to disclose whether or not the eluate was deposited by a defined and controlled method. Accordingly, Zhang *et al.* does not disclose dispensing a defined and controlled volume of fluid to form an array of spots and provides no disclosure of an array of spots that have reproducible spot-to-spot characteristics.

In a determination of the novelty of a claim, the cited reference must disclose the claim elements in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. Zhang *et al.* discloses a method for concentrating and desalting a sample, not dispensing a defined and controlled volume of fluid. Since Zhang *et al.* does not disclose all elements of the methods recited in the claims, the reference cannot anticipate the claimed methods.

The Office Action states that the "accuracy of the volume [in Zhang *et al.*] is given with the same precision" as the instant specification. The statement in the specification to which the Office Action points is a teaching of dispensing 3-HPA matrix solution without sample analyte, not to dispensing of analyte. Claim 1, in contrast, recites dispensing a defined and controlled volume of fluid that contains a solvent containing sample material. Thus the lack of precision alleged by the Office Action may apply to delivery of matrix without sample, but does not apply to delivering a defined and controlled volume of sample-containing fluid. Accordingly, the statement in the specification relied on by the Office Action is inapplicable to the rejected claims. Furthermore, the claims recite delivery of a "defined and controlled volume" such that *mass spectra of the sample obtained from each spot are reproducible within the array of spots*.

Furthermore, Zhang *et al.* discloses nothing regarding the precision of dispensing fluid onto the surface of a substrate. The meaning of the terms

"accuracy" and "precision" should not be conflated in order to make it appear that the disclosure of Zhang *et al.* is identical to the claimed methods. "Accuracy" refers to the degree to which a value represents the true value. Zhang *et al.* and the matrix solution-dispensing statement in the specification pointed to by the Office Action disclose an accuracy of about 5 nl. "Precision" refers to the reproducibility of a quantifiable result. Thus, the accuracy of the amount of liquid dispensed is not the same as the precision and reproducibility of liquid dispensed. Zhang *et al.* discloses nothing about the precision of delivering a volume; Zhang *et al.* is directed to increasing sensitivity (*i.e.* detection limit) by concentrating and desalting a sample; Zhang *et al.* is not directed to methods involving delivery of a defined and controlled volume.

Zhang *et al.* discloses nothing about dispensing a defined and controlled volume or spot-to-spot reproducibility. The disclosure by Zhang *et al.* of elution and spotting of volume that is "about 5 nl" is not a disclosure of delivery of a defined and controlled volume.

Disclosure in the specification of dispensing matrix solution with an accuracy that is ~5 nL does not limit or reduce the degree of reproducibility achieved by delivering a defined and controlled volume of **analyte**. Accordingly, the statement by Zhang *et al.* regarding the accuracy of spotting a volume of eluent is inapplicable to the claim element of dispensing a defined and controlled volume to form an array of spots having reproducible spot-to-spot characteristics.

Reproducible Mass Spectra Within an Array of Spots

Claims 1 and 25 recite that the volumes delivered are defined and controlled such that mass spectra of the material obtained from each spot are reproducible within the array of spots. Zhang *et al.* does not disclose delivery of a plurality of samples such that mass spectra that are reproducible within an array of spots. Zhang *et al.* does not even disclose preparation of an array of spots. Zhang *et al.* discloses a sample concentration and desalting method that

has "reproducibility" in that quantitation of sample compared to an internal sample is reproducible. This is **not** disclosure of a method of delivering a defined and controlled volume.

As noted, Zhang *et al.* discloses a method for desalting and concentrating samples, not a method for delivery of a defined and controlled volume nor preparation of a substrate with an array of spots where the spots exhibit spot-to-spot reproducibility. In Zhang *et al.*, there is no need for the volume dispensed to be defined and controlled, because Zhang *et al.* is concerned with the amount and condition of the sample eluted (i.e., concentrated and desalted sample), not the volume of eluant used to elute the sample nor the volume of eluant dispensed onto the target. Thus, the "reproducibility" disclosed by Zhang *et al.* refers to reproducibility of the sample preparation, and not reproducibility of mass spectra of an array of spots. In contrast, "reproducible" as recited in the claims refers to MALDI mass spectra that are reproducible within an array of spots.

The Office Action asserts that reproducibility of MALDI spectra obtained directly from the spots is "intrinsic" to the substrate having the same wells and the same volumes of sample placed in the wells (~5 nL). Since Zhang *et al.* does not disclose this, it appears that the Office Action is asserting that Zhang *et al.* ***inherently*** discloses mass spectra of the sample obtained from each spot that are reproducible within the array of spots. There is no disclosure in the reference of a substrate having identical wells nor of the same 5 nL volumes deposited in each well. Further, Zhang *et al.* does not disclose collecting mass spectra from two or more spots of an array nor any comparison thereof. Zhang *et al.* does not even disclose an array of spots on a substrate. The reference also does not disclose spots on an array deposited in defined and controlled volumes.

In order to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described

in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. MPEP §2112; *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Zhang *et al.* never discloses mass spectra from an array of spots on a substrate. Zhang *et al.* discloses nothing regarding delivery of defined and controlled volumes, nor a resulting substrate with spots resulting from deposition of a defined and controlled volume. Zhang *et al.* is directed to elution of desalted sample from a column, not to delivery of a defined and controlled delivery of volumes of eluant to a plurality of loci on a substrate. Zhang *et al.* describes a method for increasing the sensitivity of mass spectrometric analyses, not to increasing reproducibility; Zhang *et al.* does not disclose a method of preparation of substrates that contain a plurality of spots resulting from delivery of defined and controlled volumes such that spot-to-spot characteristics are reproducible from spot to spot.

Because Zhang *et al.* does not disclose any method for delivery of defined and controlled volumes, nor a substrate with a plurality of spots deposited by a defined and controlled method, there can be no disclosure in Zhang *et al.*, explicit or inherent, of a method for preparation of an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array by delivering a defined and controlled 0.2 to 20 nanoliter volume of the fluid to a plurality of loci on a substrate to produce an array of spots of sample material on the substrate such that spot-to-spot characteristics are reproducible in the array, and performing mass spectrometry analysis of the sample material at each location of the array, where mass spectra of the sample obtained from each spot are reproducible within the array of spots. Accordingly, this reference does not communicate to one of ordinary skill in the art that (1) a plurality of spots of material are delivered, where each has a defined and controlled volume and (2) that spot-to-spot characteristics are reproducible in the array such that

mass spectra reproducible between spots are necessarily present in the cited reference. Thus, Zhang *et al.*, does not explicitly or inherently disclose all elements of the claimed methods.

Moving a Vesicle to Two or More Positions

Claim 1 recites moving a vesicle to each of a set of positions whereby fluid is dispensed at each location. Claim 25 recites delivering fluid at a first location and moving the vesicle to a second location to dispense material along an array of locations. Zhang *et al.* does not disclose moving a vesicle to multiple positions on adjacent to the surface of a substrate. Zhang *et al.* does not disclose an array of spots on which mass spectrometry is performed.

The Office Action asserts that:

> It is absolutely clear from Figure 1 and its caption that the vesicle is moved from spot to spot to repeat these steps for each location (each well) of the multi-well holder ...

The Office Action fails to support its above statement by pointing to any specific portion of Zhang *et al.* that discloses movement of a vesicle. In Figure 1, Zhang *et al.* disclose a MALDI sample micro-concentration/desalting/matrix addition device, including a MALDI-MS sample holder. The caption of Figure 1 states in relevant part that "the sample volume spotted on the target was ~5nl per fraction." Nothing in Figure 1, nor any word or phrase in its caption, nor any other portion of Zhang *et al.* discloses movement of a vesicle. Further, no portion of Figure 1 nor any word or phrase in its caption, nor any other portion of Zhang *et al.* discloses repeating delivery of fluid for each location of a multi-well MALDI sample holder.

In holding a claim anticipated, "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. There is no disclosure in Zhang *et al.* of delivering fluid at a first location and moving the vesicle to a second location to dispense material along an array of locations. Therefore, Zhang *et al.* also does not disclose an element

of moving a vesicle to each of a set of positions adjacent to the surface of a substrate or moving a vesical to a second position next to a first location to dispense material along an array of locations, as recited in claims 1 and 25, respectively.

Therefore, because Zhang *et al.* fails to disclose delivering a defined and controlled volume to a substrate without contacting a substrate or moving a vesicle to each of a set of positions adjacent to the surface of a substrate or moving a vesical to a second position next to a first location to dispense material along an array of locations, Zhang *et al.* does not anticipate claim 1 or 25 nor any claims dependent thereon.

THE REJECTIONS UNDER 35 U.S.C. § 103(a)

The Rejection of Claims 11-13, 29, 31-34, 40-42, 47, 51, 54-59, 61, 63-72, 82-85 and 87-94 as Obvious over Zhang *et al.* and Nelson *et al.*

Claims 11-13, 29, 31-34, 40-42, 47, 51, 54-59, 61, 63-72, 82-85 and 87-94 are rejected as unpatentable over Zhang *et al.* and Nelson *et al.* because the teachings of Nelson *et al.* regarding guide pins, an ink-jet applicator, and an automated delivery flow system allegedly combine with the teachings of Zhang *et al.* to render the claims obvious. The rejection is respectfully traversed.

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by

combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v. Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesh*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

References

Zhang *et al.*

The reference by Zhang *et al.* is described above.

Nelson *et al.*

Nelson *et al.* teaches methods for carrying out surface plasmon resonance mass spectrometry. The method taught by the reference includes use of a molecular interaction analysis (IA) surface containing antibodies, passing sample through a flow channel containing the antibodies, and detecting binding of the antibodies by a change in the intensity of the reflected light versus angle of incidence. One such IA surface of the reference is an IA sensor chip with a plurality of interactive surfaces in contact with individual flow cells, where samples and reagents are delivered to the chip surface by an automated flow system.

The reference teaches that the IA sensor chip can be used as the sample stage for mass spectrometry. The reference provides that matrix can be added to the chip using a matrix applicator containing multiple surfaces to which matrix is applied, and then the matrix applicator surfaces are placed in contact with the sensor chip. Matrix can also be applied using an ink jet applicator where the "ink" contains matrix.

Claims

Claims 11-13

Claim 11 is directed to the method of claim 1, discussed above, wherein the vesicle is part of a vesicle assembly having a plurality of vesicles arranged into a matrix for dispensing fluid to a first plurality of locations onto said substrate surface. Claims 12 and 13 depend from claim 11.

Claim 29

Claim 29 is directed to the method of claim 25, discussed above, wherein said step of performing mass spectrometry includes the step of performing a time of flight mass spectrometry analysis.

Claims 31-34 and 92

Claim 31 is directed to a system for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the array, comprising:

a vesicle having a distal end suitable for carrying a nanoliter of fluid;

a movable arm having a distal portion mounted to move said vesicle;

a controller for moving said arm to dispose said vesicle adjacent to a first location on said surface of the substrate and for controlling said vesicle to deliver a defined and controlled 0.2 to 20 nanoliter volume of the fluid at said first location of said surface of the substrate; and

a mass spectrometer for analyzing said material deposited on said surface of said substrate, wherein mass spectra of the sample material obtained from each spot are reproducible within the array of spots.

Claims 32-34 and 92 depend from claim 31.

Claims 40-42, 47, 51, 54-59, 61, 63-69 and 93

Claim 40 is directed to a method for dispensing sub to low nanoliter volumes of a material as an array onto the surface of a substrate, comprising the steps of:

(a) providing an assembly having a plurality of vesicles arranged in the form of an array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material;

(b) aligning the vesicles at a first set of locations adjacent to the surface of the substrate without contacting the surface with the vesicles;

(c) using mechanical pressure, controlling each of the chambers to eject a defined and controlled 0.2 to 20 nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles, whereby an array of spots of the fluid is deposited on the surface of the substrate, such that spot-to-spot characteristics are reproducible in the array; and

(d) providing the resulting substrate with the array of material deposited thereon to a mass spectrometer and determining information representative of the composition of the deposited material, wherein mass spectra of the material obtained from each spot containing analyte are reproducible within the array of spots.

Claims 41, 42, 47, 51, 54-59, 61, 63-69 and 93 depend from claim 40.

Claims 70-72 and 94

Claim 70 is directed to a method for dispensing nanoliter volumes of a material as an array on the surface of a substrate and analyzing the material in the array, comprising the steps of:

(a) providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, wherein each vesicle

comprises a solid shaft of material having an end for retaining a nanoliter volume of fluid;

(b) loading a nanoliter volume of fluid comprising a liquid material from a fluid source onto the end of the vesicles of the pin assembly;

(c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to a surface of the substrate without contacting the surface with the vesicles;

(d) contacting the loaded fluid to the surface of the substrate aligned with the vesicles to deposit a defined and controlled 0.2 to 20 nanoliter volume at each location, whereby an array of spots of material on the surface of the substrate is formed, such that spot-to-spot characteristics are reproducible in the array; and

(e) analyzing the array of material on the surface of the substrate by mass spectrometry, wherein:

mass spectra of the material obtained from each spot are reproducible within the array of spots;

the substrate comprises matrix material;

the fluid comprises analyte material;

the fluid of analyte material at the end of the vesicles is contacted with the evaporated matrix material on the surface of the substrate to dissolve the matrix material with the analyte material and thereby deposit a mixture of matrix and analyte material.

Claims 71, 72 and 94 depend from claim 70.

Claims 87-91

Claims 78-91 are directed to the method of claim 1, where claim 87 further provides that the vesicle is part of an assembly of vesicle elements, wherein each vesicle comprises an interior chamber holding the 0.2 to 20 nanoliter volumes of fluid, and claim 88 depends from claim 87.

Claim 89 further provides that the vesicle has an interior chamber and forms part of an assembly comprising a plurality of vesicles and a transducer element mounted to each vesicle for driving fluid through the interior chamber to eject fluid by deforming the chamber; and

the transducer element deforms the chamber with sufficient pressure to spray the fluid from the pin or to cause a drop of fluid to extend from the chamber so that fluid can be passed to the substrate by contacting the drop to the surface of the substrate.

Claim 90 further provides that the method of claim 1 is automated.

Claim 91 further provides that the mass spectrometry format is matrix assisted laser desorption ionization mass spectrometry.

Analysis

It is respectfully submitted that the teachings of the references singly or in any combination thereof does not result in claimed methods or systems. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 11-13, 40-42, 47, 51, 54-59, 61, 63-72, 82-85, 87-89, 93 and 94

Claims 11-13, 40-42, 47, 51, 54-59, 61, 63-72, 82-85, 87-89, 93 and 94 are directed to methods of forming an a array of material on the surface of a substrate, using either a plurality of vesicles arranged in a matrix or an array, or using an assembly of vesicles. In each of the claimed methods, the plurality or assembly of vesicles are disposed adjacent to the surface of the substrate without contacting the surface of the substrate.

The combination of teachings of the references does not result in the instantly claimed methods and systems.

As discussed below, the combination of teachings of the references fails to teach or suggest delivery of a defined and controlled volume nor delivery of the volume of material without contacting the surface of a substrate nor a system containing a substrate resulting from such delivery.

Disposing or Aligning a Plurality or Assembly of Vesicles Adjacent to the Surface of the Substrate Without Contacting the Surface of the Substrate

As acknowledged by the Office Action, Zhang *et al.* does not teach or suggest a plurality of vesicles or an assembly of vesicles. Zhang *et al.* also does not teach or suggest disposing vesicles adjacent to the surface of the substrate without contacting the surface of the substrate. Thus, Zhang *et al.* does not

teach or suggest disposing or aligning plurality or assembly of vesicles adjacent to the surface of the substrate without contacting the surface of the substrate.

Nelson *et al.* teaches that matrix can be added to a chip by contacting the chip with a matrix applicator containing multiple surfaces to which matrix has been applied. Nelson *et al.* provides that as an alternative to using the multiple surface matrix applicator, matrix can instead be applied using an ink jet applicator where the "ink" contains matrix. Thus, Nelson *et al.* does not teach or suggest disposing or aligning a plurality or assembly of vesicles adjacent to the surface of the substrate without contacting the surface of the substrate.

The combination of Zhang *et al.* and Nelson *et al.* also does not teach or suggest disposing or aligning a plurality or assembly of vesicles adjacent to the surface of the substrate without contacting the surface of the substrate. Zhang *et al.* is silent regarding both a plurality or assembly of vesicles and disposing vesicles adjacent to the surface of the substrate without contacting the surface of the substrate. Thus, Zhang *et al.* adds nothing to that which is missing in Nelson *et al.*

In order to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03; *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). The cited references, neither alone or combined, teach or suggest disposing or aligning a plurality or assembly of vesicles adjacent to the surface of the substrate without contacting the surface of the substrate. The cited references do not teach or suggest all elements of claims 11-13, 40-42, 47, 51, 54-59, 61, 63-72, 82-85, 87-89, 93 and 94, and therefore, the references, alone or combined, cannot render the claims *prima facie* obvious.

The Office Action appears to not allege that either Zhang *et al.* or Nelson *et al.*, or a combination thereof, teaches or suggests disposing or aligning a

plurality or assembly of vesicles adjacent to the surface of the substrate without contacting the surface. Instead, the Office Action appears to assert that a plurality of vesicles (capillaries of Zhang *et al.* or ink-jet applicators of Nelson *et al.*) would have been obvious because use of a plurality "is an advantage regarding the speed and efficiency of the method of forming MALDI-MS substrate." This statement is an assertion of a fact not taught or suggested by either Zhang *et al.* or Nelson *et al.* Accordingly, this statement represents an entry of evidence into the record by judicial notice.

The Examiner cannot take judicial notice of facts outside the record that are not capable of instant and unquestionable demonstration. In an obviousness rejection, deficiencies of the cited references cannot be remedied by general conclusions about what is "basic knowledge" or "common sense" to one of ordinary skill in the art. *In re Zurko*, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001). With respect to core factual findings in a determination of patentability, an Office Action cannot simply reach conclusions based on its own understanding or experience — or on its assessment of what would be basic knowledge or common sense. Rather, the Office Action must point to some concrete evidence in the record in support of these findings. *Zurko*, at 1697. If an applicant traverses the an assertion of judicial notice, the Examiner must provide documentary evidence in the next Office Action if the rejection is to be maintained. See MPEP §2144.03; 37 CFR §1.104(c)(2), which states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The elements that the Examiner urges any one of ordinary skill in the art would have done in the context of the subject matter of this application are not "capable of instant and unquestionable demonstration as being 'well-known' in the art." In this instance, there is no evidence that using a plurality of vesicles "is an obvious advantage regarding the speed and efficiency of the method of

forming MALDI-MS substrate." This statement alleges the manner in which one of ordinary skill in the art would choose to increase speed and efficiency of MALDI-MS substrate production. Improvements in MALDI-MS substrate production are neither basic knowledge nor arise simply from common sense, and methods of MALDI-MS substrate production fall outside of the expertise of the PTO to determine in the absence of supporting evidence. Accordingly, documentary evidence supporting the contention asserted by judicial notice should be provided. In the absence of such supporting documentary evidence, the Office Action has not established the proposed modification of the references, and, therefore has not established that all the claim limitations are taught or suggested.

Defined and Controlled Volume to produce a substrate with an array of spots with reproducible spot-to-spot characteristics such that mass spectra among the spots are reproducible

Even if judicial notice could be established with sufficient supporting evidence, the combination of Zhang *et al.*, Nelson *et al.*, and the evidence asserted by judicial notice does not teach or suggest dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array. As discussed above, Zhang *et al.* does not teach or suggest dispensing, without contacting the surface, a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array, where mass spectra obtained from each spot are reproducible within the array of spots. The evidence asserted by judicial notice has no bearing on defined and controlled dispensing nor on the reproducibility of spot characteristics.

Nelson *et al.* does not provide that which is lacking in Zhang *et al.* and the evidence asserted by judicial notice. Nelson *et al.* teaches a sample flow cell on a substrate and dispensing matrix on the surface of the substrate. Nelson *et al.* provides no teaching or suggestion of dispensing a defined and

controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array. Because Nelson *et al.* is silent on this claim element, combining Nelson *et al.* with Zhang *et al.* and the evidence asserted by judicial notice provides no additional teaching or suggestion of this claim element.

Nelson *et al.* teaches measuring mass spectra from multiple flow cells. Nelson *et al.* provides no teaching or suggestion of a methods in which defined and controlled volumes are delivered such that mass spectra obtained from each spot are reproducible within the array of spots. Because Nelson is silent on this claim element, combining Nelson *et al.* with Zhang *et al.* and the evidence asserted by judicial notice provides no additional teaching or suggestion of this claim element.

Zhang *et al.*, Nelson *et al.*, and evidence asserted by judicial notice, neither alone nor combined, teaches or suggests dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array, or mass spectra obtained from each spot that are reproducible within the array of spots. Therefore, because the combination of teachings of the cited references does not result in the claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

There would have been no motivation to have combined the teachings of the cited references nor would there have been motivation to do that which applicant has done

Even if all elements of the claimed methods were taught or suggested by the evidence of record, one of ordinary skill in the art would not have been motivated to have combined the teachings cited references in such a way to arrive at the claimed methods or systems. Zhang *et al.* teaches a sample concentration and desalting method, where eluted sample is spotted onto a MALDI target (page 1768, first paragraph). Zhang *et al.* teaches that these

goals are accomplished by first introducing sample into a C_{18}-packed fused silica capillary, washing the salts off with water, eluting a peptide sample with an organic solvent phase containing MALDI matrix, and directly spotting eluate onto a MALDI target (page 1768). Thus, Zhang *et al.* teaches the desirability of sample elution in preparing the sample for mass spectrometry. Zhang *et al.* fails to teach or suggest anything regarding delivery of a defined and controlled volume nor delivery without contacting the surface nor delivery of a plurality of samples to a substrate.

Nelson *et al.* teaches collecting real-time information regarding molecular interactions, as well as capturing an analyte from a sample, resulting in localization and concentration of the sample for subsequent mass spectrometry (column 7, lines 15-20). As part of preserving concentrated sample and real-time monitoring sample localization and concentration, Nelson *et al.* teaches that best sensitivity is achieved when ligands are sampled directly from the sensor surface rather than eluted into a mass spectrometer (column 9, lines 29-31). In the case of MALDI, matrix is added to the sensor surface (column 10, lines 19-21). Thus, Nelson *et al.* teaches the desirability of not eluting sample from the sample capture surface, and adding matrix directly to the surface for mass spectrometry.

The Office Action appears to suggest that one of ordinary skill in the art would have been motivated to have modified the method of Zhang *et al.* with the teachings of Nelson *et al.* regarding use of (1) an ink-jet applicator and (2) full automation. To establish a *prima facie* case of obviousness, there must be a teaching or suggestion to modify or combine the references to arrive at the claimed subject matter. "Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." *In re Fritch*, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (emphasis original). "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the

desirability of the modification." *In re Fritch*, at 1783-84. Without the teachings of the prior art suggesting the combination, it is impermissible to pick and choose among isolated disclosures in the prior art to conclude that the claimed subject matter is obvious. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP §2143; *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Ink-Jet Applicator

The Office Action does not point to teachings or suggestions of either Zhang *et al.* or Nelson *et al.* regarding the desirability for using an ink-jet applicator in an elution method. Moreover, no teachings or suggestions for the modifications proposed by the Office Action exist in either Zhang *et al.* or Nelson *et al.* Zhang *et al.* teaches only the use of syringe pumps in the elution method, and suggests nothing about desirable devices or methods for dispensing eluate onto a target. Nelson *et al.* teaches the desirability of not eluting the bound sample, but instead contacting the bound sample with matrix, using an ink-jet applicator. The ink-jet applicator of Nelson *et al.* cannot be picked out of its context in Nelson *et al.* and used in a process that includes eluting a sample onto a substrate. That is, the ink-jet applicator of Nelson *et al.* cannot be used in a method inconsistent with the teachings of Nelson *et al.*, particularly since Zhang *et al.* lack any teachings of desirability of such a use. Without the teachings of the references suggesting the combination, such a proposed modification is impermissible.

Automation

The Office Action does not point to teachings or suggestions of either Zhang *et al.* or Nelson *et al.* regarding the desirability of automating the method of Zhang *et al.* as proposed by the Office Action. Moreover, no teachings or suggestions for the modifications proposed by the Office Action exist in either

Zhang *et al.* or Nelson *et al.* Nelson *et al.* teach the desirability of automating delivery of a sample to a flow cell of a chip that serves as the mass spectrometry target. Zhang *et al.* teach spotting eluate onto a mass spectrometry target. It is unclear how one of ordinary skill in the art would modify a spotting method using a flow cell method without simply replacing the spotting method with the flow cell method, and the Office Action does not describe how such a modification would be implemented in the method of Zhang *et al.* The automated method of Nelson *et al.* takes advantage of not eluting sample from the chip surface. If the method of Zhang *et al.* were replaced by the automated method of Nelson *et al.*, sample would no longer be eluted from the C_{18} capillary and spotted onto a mass spectrometry substrate. Thus, modifying the method of Zhang *et al.* by automating it in accordance with Nelson *et al.*, would eliminate elution and spotting onto a mass spectrometry substrate. Zhang *et al.* teaches elution in the sample preparation method. Thus, the proposed automation of Zhang *et al.* would render the method of Zhang *et al.* unsatisfactory for the purposes taught by Zhang *et al.* Accordingly, there can be no suggestion or motivation to make the proposed modification.

In sum, the Office Action uses two elements from Nelson *et al.* to modify the method of Zhang *et al.*, but the references do not teach or suggest such modifications. Further, the teachings of the cited references, if anything, would discourage the modifications proposed by the Office Action. Therefore, the reference of Zhang *et al.* cannot be combined with the reference of Nelson *et al.* Accordingly, the Office Action has not established a *prima facia* case of obviousness for any claim rejected under this combination of references.

Finally, even if there were such motivation, the combination of these teachings do not resulting in the instantly claimed methods or systems.

Claims 31-34 and 92

Claims 31-34 and 92 recite systems containing a vesicle having a distal end, a movable arm having a distal portion mounted to move the vesicle, a

controller for moving the arm and for controlling the vesicle to deliver a defined and controlled volume to the surface of a substrate, and a mass spectrometer for analyzing material deposited on the surface of the substrate, where mass spectra from each spot are reproducible within the array of spots.

No Basis is Provided for Rejecting These Claims

The Office Action does not communicate the basis for the obviousness rejection of these claims such that the issues can be identified and addressed by the Applicant. The Office Action does not point to Zhang *et al.* or Nelson *et al.* for a teaching or suggestion of a movable arm. The Office Action does not point to Zhang *et al.* or Nelson *et al.* for a teaching or suggestion of a controller for moving a movable arm. The Office Action does not point to Zhang *et al.* or Nelson *et al.* for a teaching or suggestion of a controller for controlling a vesicle to deliver a defined and controlled volume to the surface of a substrate.

It is important for an Office Action to properly communicate the basis for a rejection so that the issues can be identified early and the Applicant can be given fair opportunity to reply. MPEP §706.02(j). The Office Action bears the initial burden of factually supporting a *prima facie* conclusion of obviousness. MPEP §2142. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03; *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

The Office Action does not allege that Zhang *et al.* or Nelson *et al.* teaches or suggests a movable arm, a controller for moving a movable arm, or a controller for controlling a vesicle to deliver a defined and controlled volume to the surface of a substrate. Thus, the Office Action does not allege that the cited references teach or suggest all elements of claim 31 or claims dependent therefrom.

The combination of teachings of the cited references does not result in the instantly claimed systems.

Even if the Office Action had asserted that Zhang *et al.* and Nelson *et al.* teach or suggest the above elements, the teachings of the cited references, alone or combined, do not teach or suggest a system that includes a vesicle having a distal end, a movable arm having a distal portion mounted to move the vesicle, a controller for moving the arm and for controlling the vesicle to deliver a defined and controlled volume to the surface of a substrate, and a mass spectrometer for analyzing material deposited on the surface of the substrate

As discussed above, Zhang *et al.* does not teach or suggest any of these elements and Nelson *et al.* does not provide that which is lacking in Zhang *et al.* Nelson *et al.* teaches measuring mass spectra from multiple flow cells. Nelson *et al.* provides no teaching or suggestion of system that includes a vesicle having a distal end, a movable arm having a distal portion mounted to move the vesicle, a controller for moving the arm and for controlling the vesicle to deliver a defined and controlled volume to the surface of a substrate, and a mass spectrometer for analyzing material deposited on the surface of the substrate.

Because Nelson is silent on these claim elements, combining Nelson *et al.* with Zhang *et al.* provides no additional teaching or suggestion of these claim elements. Accordingly, the cited references cannot establish a *prima facie* obviousness rejection of claims 31-34 and 92.

Claims 29, 90 and 91

Claims 29 and 91

Claim 29 is directed to the method of claim 25 where mass spectrometry includes time of flight (TOF) mass spectrometry analysis. Claim 91 is directed to the method of claim 1 where mass spectrometry includes matrix assisted laser desorption ionization mass spectrometry (MALDI). Both Zhang *et al.* and Nelson *et al.* teach MALDI-TOF mass spectrometry (see, e.g., title of Zhang *et*

al.). Zhang *et al.* and Nelson *et al.*, alone or combined, do not teach or suggest all claim elements of claims 1 and 25.

As discussed above, Zhang *et al.* does not teach or suggest delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible, nor reproducible mass spectra within an array of spots.

Nelson *et al.* does not provide that which is lacking in Zhang *et al.* Nelson *et al.* teaches a sample flow cell on substrate and dispensing matrix on the surface of the substrate. Nelson provides no teaching or suggestion of dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array nor delivery without contacting. Regarding mass spectra, Nelson *et al.* teaches measuring mass spectra from multiple flow cells. Nelson *et al.* provides no teaching or suggestion regarding mass spectra obtained from spot on an array that are reproducible within the array Because Nelson is silent with respect to these claim elements, combining the teachings of Nelson *et al.* with those of Zhang *et al.* does not result in the

Thus the teachings of Zhang *et al.* and Nelson *et al.*, singly or in any combination thereof do not result in a method including a step of dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array such that mass spectra obtained from each spot that are reproducible within the array of spots.

Claim 90

Claim 90 is directed to the method of claim 1 that is automated. As above, the teachings of the cited references, singly or combined, do not result in all elements of claim 1. Furthermore, the teachings of Zhang *et al.* and Nelson *et al.*, alone nor combined, do not result in method including a step of dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array, or that mass spectra obtained from each spot that are reproducible within the array of spots.

Further, as stated above, no teachings or suggestions for the automation modification proposed by the Office Action exist in either Zhang *et al.* or Nelson *et al.* Further, if the method of Zhang *et al.* were replaced by the automated method of Nelson *et al.*, sample would no longer be eluted from the C_{18} capillary nor spotted onto a substrate. Thus, modifying the method of Zhang *et al.* by automating it in accordance with Nelson *et al.*, would eliminate elution. Zhang *et al.* teaches the desirability of elution in the sample preparation method. Thus, the proposed modification of Zhang *et al.* would render the method of Zhang *et al.* unsatisfactory for the purposes taught by Zhang *et al.* Accordingly, there can be no suggestion or motivation to make the proposed modification.

Therefore the Examiner has failed to set forth a *prima facie* case of obviousness.

The Rejection of Claims 5, 45, 46, 48-50 and 78 as Obvious over Zhang I, Nelson *et al.* and Zhang II

Claims 5, 45, 46, 48-50 and 78 are rejected as allegedly obvious over Zhang *et al.*, J. Mass Spectrom. 30:1768-1771 (1995) (hereinafter Zhang I), Nelson *et al.*, U.S. Pat. No. 5,955,729, and Zhang *et al.*, J. Mass Spectrom. 31:1039-1046 (1996) (hereinafter Zhang II) because it allegedly would have been obvious to have used the matrix-precoated cellulose membrane of Zhang II with the combination of Zhang I and Nelson *et al.* described above.

References

Zhang I and Nelson *et al.*

Zhang I and Nelson *et al.* are described above.

Zhang II

Zhang II teaches continuous deposit of capillary electrophoresis effluent on a matrix-precoated cellulose membrane, with subsequent analysis using MALDI mass spectrometry. Zhang II teaches preparation of the matrix-precoated cellulose membrane by applying a solution containing matrix to a cellulose membrane fixed to the surface of a MALDI target plate to cover the membrane surface and then placing the membrane in a desiccator. Zhang II

teaches mounting the membrane/target to a movable stage in contact with a capillary membrane strip. Zhang II teaches that the sample was loaded electrokinetically in conjunction with movement of the target plate.

Claims

Claim 5 is directed to a method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing material for deposition;

disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;

providing mechanical pressure to the interior of the vesicle to eject from said chamber a defined and controlled 0.2 to 20 nanoliter volume of the fluid to dispense solvent containing matrix material at said first location of said surface of the substrate, wherein the matrix material is for matrix-assisted laser desorption mass spectrometry;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled 0.2 to 20 nanoliter volume of solvent containing a matrix material is dispensed at each locus of the array;

waiting a predetermined period of time to allow the solvent containing the matrix material to evaporate on the surface of the substrate thereby depositing the matrix material on the surface;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled 0.2 to 20 nanoliter volume of fluid containing an analyte material is dispensed onto said evaporated matrix material at each locus of the array to dissolve with said matrix material and to form a crystalline structure at each locus of the substrate surface such that spot-to-spot characteristics are reproducible in the array;

performing mass spectrometry analysis of the sample material at each location of the array, wherein mass spectra of the material obtained from each spot are reproducible within the array of spots.

Claims 45-46 and 48-50 are directed to the method of claim 40, where claim 45 further recites waiting a predetermined period of time to allow solvent comprising the matrix material to evaporate from the fluid ejected onto the surface of the substrate leaving the matrix material deposited on the surface, and then repeating steps of (a) through (c) of claim 40 at the same locations on which the matrix material is deposited, wherein the chambers of the vesicles in

the assembly contain a solvent comprising an analyte material, which upon ejection on the array of matrix material dissolves into the matrix.

Claim 46 recites that the method of claim 40 further includes

(d) moving the assembly of step (a) to align the vesicles at a second set of locations adjacent to the surface of the substrate;
(e) repeating step (c); and
(f) optionally repeating steps (d) and (e) to dispense fluid at additional sets of locations on the surface of the substrate, wherein steps of (a) through (f) are repeated at the same locations on which the matrix material is deposited, wherein the chambers of the vesicles in the assembly contain a solvent comprising an analyte material, which upon ejection on the array of matrix material dissolves into the matrix.

Claim 48 further recites that the fluid comprises an analyte in a solvent, and includes the further step of waiting a predetermined period of time to allow the solvent comprising analyte to evaporate from the fluid ejected onto the surface of the substrate leaving the analyte material deposited on the surface. Claim 49 is directed to the method of claim 49, further comprising repeating steps of (a) through (c) are repeated at the same locations at which analyte is deposited, wherein the chambers of the vesicles in the assembly contain a solvent comprising a matrix material, which upon ejection onto the array of analyte dissolves into the analyte.

Claim 50 recites that the method of claim 40 further includes

(d) moving the assembly of step (a) to align the vesicles at a second set of locations adjacent to the surface of the substrate;
(e) repeating step (c); and
(f) optionally repeating steps (d) and (e) to dispense fluid at additional sets of locations on the surface of the substrate, where the fluid comprises an analyte in a solvent;

the method includes the further step of waiting a predetermined period of time to allow the solvent comprising analyte to evaporate from the fluid ejected onto the surface of the substrate leaving the analyte material deposited on the surface; and
steps of (a) through (f) are repeated at the same locations at which analyte is deposited, wherein the chambers of the vesicles in the assembly contain a solvent comprising a matrix material, which upon ejection onto the array of analyte dissolves into the analyte.

Analysis

Claims 5, 45 and 46, thus are directed to methods in which a vesicle ejects matrix onto the surface of a substrate, and then steps are repeated with the vesicles ejecting analyte at the same locations on which matrix material is deposited. Claims 49, 50 and 78 are directed to methods in which a vesicle ejects analyte onto the surface of a substrate, and then steps are repeated with the vesicles ejecting matrix such that evaporated analyte material contacts the matrix material. Claim 48 is directed to a method of waiting a predetermined period of time to allow solvent to evaporate. All claims recite ejecting a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array. All claims also recite mass spectra from each spot are reproducible within the array of spots. The cited references do not render the methods of these claims obvious because the cited references, alone or combined, do not teach or suggest all elements of the claims.

Reproducible Spot-to-Spot Characteristics and Reproducible Mass Spectra

None of Zhang I, Nelson *et al.* and Zhang II, singly or in any combination thereof, teaches or suggests the methods of the rejected claims. As discussed above, Zhang I and Nelson *et al.*, singly or in combination, do not teach or suggest delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible nor that resulting mass spectra are reproducible within an array of spots.

Zhang II does not cure these deficiencies. Zhang II teaches deposition of sample onto a matrix-precoated membrane nor does Zhang II teach delivery of a defined and controlled volume. Zhang II does not teach or suggest an array of spots. Accordingly, Zhang II does not cure the deficiencies in the teachings of Zhang I and Nelson *et al.*. Therefore, the combination of teachings of the cited references does nor result in the claimed methods.

Separately Ejecting Matrix and Analyte with the Same Vesicle

Claims 5, 45-46, 49-50 and 78 recite methods in which matrix and analyte are ejected onto a substrate surface in separate steps using the same vesicle. The cited references, alone or combined do not teach or suggest such a method.

Zhang I teaches eluting analyte onto a substrate surface using an eluent containing matrix. Thus, Zhang I teaches applying analyte and matrix to a substrate in the same step. Zhang I does not teach or suggest ejecting matrix and analyte onto a substrate surface in separate steps using the same vesicle.

Nelson *et al.* teaches applying analyte to a substrate by flowing a sample over a substrate surface containing an antibody. Nelson *et al.* teaches applying matrix to the substrate by contacting the substrate with a matrix applicator or using an ink-jet applicator. Thus, Nelson *et al.* teaches using different instrumentalities to eject analyte and matrix onto the surface of a substrate. Nelson *et al.* does not teach or suggest ejecting matrix and analyte onto a substrate surface in separate steps using the same vesicle.

Zhang II teaches pre-coating a membrane with MALDI matrix by covering the membrane with a matrix-containing solution. Zhang II teaches applying analyte to the membrane by electrokinetically loading sample from a capillary contacting the membrane strip. Thus, Zhang II teaches using different instrumentalities to eject analyte and matrix onto the surface of a substrate. Zhang II does not teach or suggest ejecting matrix and analyte onto a substrate surface in separate steps using the same vesicle.

None of the references teaches or suggests ejecting matrix and analyte onto a substrate surface in separate steps using the same vesicle. No combination of the references teaches or suggests ejecting matrix and analyte onto a substrate surface in separate steps using the same vesicle. Thus, the cited references, alone or combined, result in the methods of any of claims 5,

45, 46, 49, 50 or 78. Accordingly, the cited references cannot establish a *prima facie* obviousness rejection of claims 5, 45, 46, 49, 50 or 78.

The Rejection of Claims 16-24 as Obvious over Zhang I and Hancock *et al.*

Claims 16-24 are rejected as obvious over Zhang I in view of Hancock *et al.*, U.S. Pat. No. 5,716,825. The Office Action asserts that the claims are obvious because Hancock *et al.* teaches the materials recited in claims 16-24, while Zhang I teaches the underlying method. This rejection is respectfully traversed.

References

Zhang I

Zhang I is described above. As noted above, Zhang I fails to teach or suggest the underlying method.

Hancock *et al.*

Hancock *et al.* teaches an integrated microfluidic nucleic acid analysis system for MALDI-TOF mass spectrometry. The system is a small unit containing a variety of features such as apertures, microchannels and reaction zones for sample manipulation. The system also includes a MALDI ionization surface, which can be made from a variety of different materials. Hancock *et al.* teaches the purpose of the system is handle and detect small amounts of sample with minimal sample loss.

Claims

Claims 16-24 are directed to the method of claim 1, where the substrate contains silicon, a metal material, a plastic material, a membrane, a polymeric material, metal-grafted polymers, or a chemically functionalized substrate material, or is functionalized with beads or with a dendritic material.

Analysis

Claims 16-24 depend from claim 1. As discussed above, Zhang I does not teach or suggest numerous elements of claim 1, including delivering a defined and controlled volume such that spot-to-spot characteristics are

reproducible such that mass spectra are reproducible within an array of spots, and depositing material on a surface without touching the surface.

Hancock *et al.* does not teach or suggest that which is missing in Zhang I. Hancock *et al.* teaches a system with a variety of features including a MALDI ionization surface. Hancock *et al.* does not teach or suggest formation of an array of spots nor delivery without touching a surface. Hancock *et al.* does not teach or suggest delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible. Therefore, the combination of Zhang I and Hancock *et al.* result in the methods of claims 16-24. Accordingly, the combination of teachings of the cited references cannot establish a *prima facie* obviousness rejection of claims 16-24.

The Rejection of Claims 60 and 86 as Obvious over Zhang I, Nelson *et al.* and Hancock *et al.*

Claims 60 and 86 are rejected as obvious over Zhang I, Nelson *et al.* and Hancock *et al.* The Office Action asserts that the claims are obvious because Hancock *et al.* allegedly teaches materials recited in claims 60 and 86, while Zhang I and Nelson *et al.* teach the underlying methods. This rejection is respectfully traversed.

References

Zhang I, Nelson *et al.* and Hancock *et al.* are described above.

Claims

Claim 60 is directed to the method of claim 40, where the substrate comprises material selected from the group consisting of silica, glass, cellulose, silicon, metal, plastic, polymer and metal-grafted polymer.

Claim 86 is directed to the method of claim 70, where the surface of the substrate is functionalized chemically, functionalized with beads or functionalized with dendrites of captured material.

Analysis

Claims 60 and 86 depend from claims 40 and 70, respectively. As discussed the combination of teachings of Zhang I and Nelson *et al.*, singly or in

any combination thereof does not result in all elements of the claimed underlying methods, including delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible.

Hancock *et al.* does not teach or suggest that which is missing in Zhang I and Nelson *et al.* Hancock *et al.* teaches a system with a variety of features including a MALDI ionization surface. Hancock *et al.* does not teach or suggest formation of an array of spots.. Hancock *et al.* does not teach or suggest delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible.

Because Hancock *et al.* is silent regarding delivering a defined and controlled volume such that spot-to-spot characteristics, including mass spectra, are reproducible, the combination of teachings of Hancock *et al.*, Zhang I and Nelson *et al.* also does not teach or suggest these elements. Therefore, the combination of Zhang I, Nelson *et al.* and Hancock *et al.* does not teach or suggest all elements of claims 60 or 86. Accordingly, the combination of teachings of the cited references does not establish a *prima facie* obviousness rejection of claims 60 or 86.

Unexpected results

Pertinent to the rejections under 35 U.S.C. §103 is the showing of unexpected results. It is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. *In re Sernaker*; 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesh*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

As discussed in previous responses the DECLARATION of record establishes results that are neither taught nor suggested by any reference of record. None of the cited references teaches or suggests that dispensing a

plurality of defined and controlled volumes would result in an array of spots, where mass spectra of the material obtained from each spot are reproducible within the array of spots. As shown in the DECLARATION of record, mass spectra of the material obtained from each spot are reproducible within the array of spots. None of Zhang, Hancock, Robotti or Jespersen *et al.*, singly or in any combination thereof teaches or suggests the increase in reproducibility from spot-to-spot by delivery or deposition of defined and controlled volumes results in uniform spectra as shown in the DECLARATION of record. Therefore, as to the claims rejected under 35 U.S.C. §103, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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